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Adam A. Dmytriw

Sherief Ghozy

Ahmad Sweid

Michel Piotin

Kimon Bekelis

See next page for additional authors

Authors

Adam A. Dmytriw, Sherief Ghozy, Ahmad Sweid, Michel Piotin, Kimon Bekelis, Nader Sourour, Eytan Raz, Daniel Vela-Duarte, Italo Linfante, Guilherme Dabus, Max Kole, Mario Martínez-Galdámez, Shahid M. Nimjee, Demetrius K. Lopes, Ameer E. Hassan, Peter Kan, Mohammad Ghorbani, Michael R. Levitt, Simon Escalard, Symeon Missios, Maksim Shapiro, Fréderic Clarençon, Mahmoud Elhorany, Rizwan A. Tahir, Patrick P. Youssef, Aditya S. Pandey, Robert M. Starke, Kareem El Naamani, Rawad Abbas, Ossama Y. Mansour, Jorge Galvan, Joshua T. Billingsley, Abolghasem Mortazavi, Melanie Walker, Mahmoud Dibas, Fabio Settecase, Manraj K. S Heran, Anna L. Kuhn, Ajit S. Puri, Bijoy K. Menon, Sanjeev Sivakumar, Ashkan Mowla, Salvatore D'Amato, Alicia M. Zha, Daniel Cooke, Justin E. Vranic, Robert W. Regenhardt, James D. Rabinov, Christopher J. Stapleton, Mayank Goyal, Hannah Wu, Jake Cohen, David Turkel-Parella, Andrew Xavier, Muhammad Waqas, Vincent Tutino, Adnan Siddiqui, Gaurav Gupta, Anil Nanda, Priyank Khandelwal, Cristina Tiu, Pere C. Portela, Natalia Perez de la Ossa, Xabier Urra, Mercedes de Lera, Juan F. Arenillas, Marc Ribo, Manuel Requena, Mariangela Piano, Guglielmo Pero, Keith De Sousa, Fawaz Al-Mufti, Zafar Hashim, Sanjeev Nayak, Leonardo Renieri, Rose Du, Mohamed A. Aziz-Sultan, David Liebeskind, Raul G. Nogueira, Mohamad Abdalkader, Thanh N. Nguyen, Nicholas Vigilante, James E. Siegler, Jonathan A. Grossberg, Hassan Saad, Michael R. Gooch, Nabeel A. Herial, Robert H. Rosenwasser, Stavropoula Tjoumakaris, Aman B. Patel, Ambooj Tiwari, and Pascal Jabbour

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Adam A. Dmytriw[1,2] | Sherief Ghozy[2] | Ahmad Sweid[3] | Michel Piotin[4] | Kimon Bekelis[5] | Nader Sourour[6] | Eytan Raz[7] | Daniel Vela-Duarte[8] | Italo Linfante[8] | Guilherme Dabus[8] | Max Kole[9] | Mario Martínez-Galdámez[10] | Shahid M. Nimjee[11] | Demetrius K. Lopes[12] | Ameer E. Hassan[13] | Peter Kan[14] | Mohammad Ghorbani[15] | Michael R. Levitt[16] | Simon Escalard[4] | Symeon Missios[5] | Maksim Shapiro[7] | Fréderic Clarençon[6] | Mahmoud Elhorany[6] | Rizwan A. Tahir[9] | Patrick P. Youssef[11] | Aditya S. Pandey[17] | Robert M. Starke[18] | Kareem El Naamani[3] | Rawad Abbas[3] | Ossama Y. Mansour[19] | Jorge Galvan[10] | Joshua T. Billingsley[12] | Abolghasem Mortazavi[13] | Melanie Walker[16] | Mahmoud Dibas[2] | Fabio Settecase[20] | Manraj K. S. Heran[20] | Anna L. Kuhn[21] | Ajit S. Puri[21] | Bijoy K. Menon[22] | Sanjeev Sivakumar[23] | Ashkan Mowla[24] | Salvatore D'Amato[1] | Alicia M. Zha[25] | Daniel Cooke[26] | Justin E. Vranic[1] | Robert W. Regenhardt[1] | James D. Rabinov[1] | Christopher J. Stapleton[1] | Mayank Goyal[22] | Hannah Wu[27,28,29] | Jake Cohen[27,28,29] | David Turkel-Parella[27,28,29] | Andrew Xavier[30,31] | Muhammad Waqas[32] | Vincent Tutino[32] | Adnan Siddiqui[32] | Gaurav Gupta[33] | Anil Nanda[33] | Priyank Khandelwal[33] | Cristina Tiu[34] | Pere C. Portela[35] | Natalia Perez de la Ossa[36] | Xabier Urra[37] | Mercedes de Lera[38] | Juan F. Arenillas[38] | Marc Ribo[39,40] | Manuel Requena[39,40] | Mariangela Piano[41] | Guglielmo Pero[41] | Keith De Sousa[42] | Fawaz Al-Mufti[43] | Zafar Hashim[44] | Sanjeev Nayak[44] | Leonardo Renieri[45] | Rose Du[2] | Mohamed A. Aziz-Sultan[2] | David Liebeskind[46] | Raul G. Nogueira[47] | Mohamad Abdalkader[48] | Thanh N. Nguyen[48] | Nicholas Vigilante[49] | James E. Siegler[49] | Jonathan A. Grossberg[50] | Hassan Saad[50] | Michael R. Gooch[3] | Nabeel A. Herial[3] | Robert H. Rosenwasser[3] | Stavropoula Tjoumakaris[3] | Aman B. Patel[1] | Ambooj Tiwari[27,28,29] | Pascal Jabbour[3] | North American Neurovascular COVID-19 (NAN-C) Consortium & Society of Vascular and Interventional Neurology (SVIN) Investigators

[1]Neuroendovascular Program, Mass General Brigham Partners, Harvard Medical School, Boston, Massachusetts, USA

[2]Neuroradiology & Neurosurgery Services, Brigham & Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

[3]Department of Neurological Surgery, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania, USA

[4]Department of Interventional Neuroradiology, Rothschild Foundation Hospital, Paris, France

[5]Department of Neurosurgery, Good Samaritan Hospital Medical Center, New York, USA

[6]Department of Interventional Neuroradiology, Pitié-Salpêtrière Hospital, Paris, France

[7]Department of Radiology, New York University Langone Medical Center, New York, New York, USA

[8]Department of Interventional Neuroradiology & Neuroendovascular Surgery, Miami Cardiac and Vascular Institute, Baptist Hospital of Miami, Miami, Florida, USA

[9]Department of Neurosurgery, Henry Ford Hospital, Detroit, Michigan, USA

[10]Department of Interventional Neuroradiology, Hospital Clinico Universitario de Valladolid, Valladolid, Spain

[11]Department of Neurosurgery, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA

[12]Department of Neurosurgery, Advocate Aurora Health, Chicago, Illinois, USA

[13]Department of Neuroscience, Valley Baptist Medical Center/University of Texas Rio Grande Valley, Harlingen, Texas, USA

[14]Department of Neurosurgery, UTMB, Houston, Texas, USA

[15]Department of Neurosurgery, Firoozgar Hospital, Tehran, Iran

[16]Departments of Neurological Surgery, Radiology, Mechanical Engineering, and Stroke & Applied Neuroscience Center, University of Washington, Seattle, Washington, USA

[17]Department of Neurosurgery, University of Michigan, Ann Arbor, Michigan, USA

[18]Department of Neurosurgery & Neuroradiology, University of Miami & Jackson Memorial Hospital, Miami, Florida, USA

[19]Department of Neurology, Alexandria University Hospital, Alexandria, Egypt

[20]Division of Neuroradiology, Vancouver General Hospital, University of British Columbia, Vancouver, British Columbia, Canada

[21]Division of Neurointerventional Radiology, Department of Radiology, UMass Memorial Medical Center, Worcester, Massachusetts, USA

[22]Calgary Stroke Program, Cumming School of Medicine, Calgary, Alberta, Canada

[23]Department of Medicine (Neurology), Prisma Health Upstate, USC, Greenville, South Carolina, USA

[24]Department of Neurological Surgery, University of Southern California, Los Angeles, California, USA

[25]Department of Neurology, UT Health Science Center, Houston, Texas, USA

[26]Department of Neurointerventional Radiology, San Francisco General Hospital, San Francisco, California, USA

[27]Department of Neurology, Brookdale University Hospital, Brooklyn, New York, USA

[28]Department of Neurology, Jamaica Medical Center, Richmond Hill, New York, USA

[29]Department of Neurology, NYU Lutheran Hospital, Brooklyn, New York, USA

[30]Department of Neurology, Sinai Grace Hospital, Detroit, Michigan, USA

[31]Department of Neurology, St. Joseph Mercy Health, Ann Arbor, Michigan, USA

[32]Department of Neurosurgery, University of New York at Buffalo, Buffalo, New York, USA

[33]Department of Neurology, Robert Wood Johnson University Hospital, New Brunswick, New Jersey, USA

[34]Department of Neurology, University Emergency Hospital Bucharest, Bucharest, Romania; "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

[35]Department of Neurology, Hospital Universitari, Bellvitge, Barcelona, Spain

[36]Stroke Unit, Neuroscience Department, Hospital Universitari Germans Trias i Pujol, Carretera Canyet s/n, Barcelona, Spain

[37]Department of Neurology, Hospital Clínic, Barcelona, Spain

[38]Department of Neurology, Hospital Clínico Universitario, Valladolid, Spain

[39]Stroke Unit, Department of Neurology, Vall d'Hebron Research Institute, Barcelona, Spain

[40]Departament de Medicina, Universitat Autónoma de Barcelona, Barcelona, Spain

[41]Department of Neuroradiology, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy

[42]Department of Neurology, Eastern Region, Northwell Health, New York, New York, USA

[43]Department of Neurology, Radiology, and Neurosurgery, Westchester Medical Center at NY Medical College, Valhalla, New York, USA

[44]Department of Radiology, University Hospital of North Midlands, Stoke-on-Trent, UK

[45]Department of Radiology, Neurovascular Unit, Careggi University Hospital, Florence, Italy

[46]Department of Neurology, Ronald Reagan UCLA Medical Center, Los Angeles, USA

[47]Department of Neurology, Marcus Stroke and Neuroscience Center, Grady Memorial Hospital, Emory University School of Medicine, Atlanta, Georgia, USA

[48]Departments of Neurology and Radiology, Boston Medical Center, Boston University School of Medicine, Boston, Massachusetts, USA

[49]Cooper Neurological Institute, Cooper University Hospital, Camden, New Jersey, USA

[50]Department of Neurosurgery|, Emory University, Atlanta, Georgia, USA

Correspondence
Adam A. Dmytriw, Neuroendovascular Program, Massachusetts General Hospital, Harvard Medical School, 55 Fruit St, Boston, MA 02114, USA.
Email: admytriw@mgh.harvard.edu

Abstract

Background and purpose: Previous studies suggest that mechanisms and outcomes in patients with COVID-19-associated stroke differ from those in patients with non-COVID-19-associated strokes, but there is limited comparative evidence focusing on these populations. The aim of this study, therefore, was to determine if a significant association exists between COVID-19 status with revascularization and functional outcomes

following thrombectomy for large vessel occlusion (LVO), after adjustment for potential confounding factors.

Methods: A cross-sectional, international multicenter retrospective study was conducted in consecutively admitted COVID-19 patients with concomitant acute LVO, compared to a control group without COVID-19. Data collected included age, gender, comorbidities, clinical characteristics, details of the involved vessels, procedural technique, and various outcomes. A multivariable-adjusted analysis was conducted.

Results: In this cohort of 697 patients with acute LVO, 302 had COVID-19 while 395 patients did not. There was a significant difference ($p < 0.001$) in the mean age (in years) and gender of patients, with younger patients and more males in the COVID-19 group. In terms of favorable revascularization (modified Thrombolysis in Cerebral Infarction [mTICI] grade 3), COVID-19 was associated with lower odds of complete revascularization (odds ratio 0.33, 95% confidence interval [CI] 0.23–0.48; $p < 0.001$), which persisted on multivariable modeling with adjustment for other predictors (adjusted odds ratio 0.30, 95% CI 0.12–0.77; $p = 0.012$). Moreover, endovascular complications, in-hospital mortality, and length of hospital stay were significantly higher among COVID-19 patients ($p < 0.001$).

Conclusion: COVID-19 was an independent predictor of incomplete revascularization and poor functional outcome in patients with stroke due to LVO. Furthermore, COVID-19 patients with LVO were more often younger and had higher morbidity/mortality rates.

KEYWORDS
COVID-19, large vessel occlusion, morbidity, mortality, stroke

INTRODUCTION

Since the first reported case in Wuhan, China, coronavirus disease 2019 (COVID-19) has been prevalent globally, with approximately 45 million cases and 730,000 deaths in the United States, up to October 8, 2021 [1]. According to the World Health Organization (WHO), there have been over 241 million cases and almost 5 million deaths worldwide [2]. Patients with COVID-19 are at higher risk of thrombotic events, with an estimated prevalence rate of 22%, which can further increase to up to 43% after admission to the intensive care unit [3]. Hypercoagulability in COVID-19 patients may be caused by disease-associated stasis, cytokine storm, dysfunctional endothelium, and platelet activation [3-5].

One form of thrombosis is acute ischemic stroke (AIS). The risk of AIS in COVID-19 patients may be elevated approximately three- to eightfold in the first 3 days of respiratory symptoms [6,7]. The reported prevalence of stroke among COVID-19 patients varies from 1.3% up to 4.9% and the rate of SARS CoV-2 infection among stroke admissions is estimated to be 3.3% [8-16]. While there have been a number of reports indicating an excess number of large vessel occlusion (LVO) strokes in patients with COVID-19 [8,17,18], there are limited data on the safety and outcomes of acute revascularization of LVO in COVID-19 patients [19,20]. To address current limitations, an international multicenter study was conducted to identify differences in the demographics and stroke characteristics of LVO patients with COVID-19 versus without COVID-19. Furthermore, we sought to evaluate whether COVID-19 has an independent association with revascularization and functional outcomes following the endovascular treatment.

MATERIALS AND METHODS

An international multicenter retrospective study of consecutively admitted COVID-19 patients with concomitant acute LVOs was performed between February 25 and December 30, 2020, across 50 international comprehensive stroke centers, from North America, Europe and the Middle East.

The institutional review boards of participating institutions reviewed and approved the study, and patient consent was waived based on the de-identified retrospective protocol with minimal risk. Diagnosis of COVID-19 was established using reverse-transcriptase PCR assays of nasopharyngeal samples for identification of SARS-CoV-2. Data will be made available by the corresponding author to qualified investigators upon reasonable request.

Data collection

Data collected included age, gender, comorbidities, clinical characteristics of the included COVID-19 patients, details of the involved vessels, procedural technique, and selected outcome measures (e.g.,

symptomatic intracerebral hemorrhage [sICH]). Onset to admission time was defined as the time from stroke onset to hospital arrival. Procedure duration was calculated as the time difference between arterial access and sheath removal. COVID-19 severity was determined based on the score and classification provided by the World Health Organization (WHO) [21]. In addition, classification of AIS subtype was performed according to the Trial of Org 10,172 in Acute Stroke Treatment (TOAST) criteria [22]. For the involved vessels, we used the same classification provided by our participating centers based on what was reported as first, second, third, and forth.

Study endpoints

Co-primary outcomes were: (i) optimal revascularization, defined as modified Thrombolysis in Cerebral Infarction (mTICI) grade 3; (ii) unfavorable functional outcome, at discharge and at 90 days, defined as modified Rankin Scale (mRS) score 3–6; and (iii) mortality at 90 days. Recanalization scoring was estimated without central imaging adjudication. Secondary outcomes were: (i) sICH, defined as reduction of four points on the National Institute of Health Stroke Scale (NIHSS) in association with any hemorrhage, at the judgment of the treating clinician; (ii) NIHSS score 24 h following mechanical thrombectomy.

Statistical analysis

All data were analyzed using R software version 4.1.1 using the packages "Rcmdr" and "glm2" [23]. Continuous variables are shown as means and standard deviation, with skewness and kurtosis tests used to evaluate the normal distribution, with comparisons made according to COVID-19 status (COVID-19 vs. non-COVID-19) using independent *t*-tests or Mann–Whitney *U*-tests, as appropriate. Categorical variables are reported as frequencies and percentages, with the chi-squared test or Fisher's exact test used for comparisons, as appropriate. Finally, univariable logistic regression was used to test covariates predictive of revascularization (mTICI grade 2b or 3), and unfavorable outcome (mRS score 3–6). Interaction and confounding were assessed through stratification and relevant expansion covariates. Whenever possible, factors predictive on univariable analysis ($p < 0.05$) were entered into a backward multivariable logistic regression analysis, and the effect of COVID-19 was assessed to be clinically relevant in all models. Regression results are expressed as odds ratios (ORs) and 95% confidence intervals (95% CIs). A p value < 0.05 was taken to indicate significance for all statistical tests. The results presented here are reported in accordance with the Strengthening the Observational Reporting of Observational Studies guidelines. Missing data were not imputed.

Data availability

The relevant anonymized patient-level data are available on reasonable request from the authors.

RESULTS

The total cohort comprised 697 patients with LVO, 302 of whom had concomitant COVID-19 (43.3%). Patients with COVID-19 had a younger mean age than those without COVID-19 (61.1 ± 15.7 years vs. 71.0 ± 15.8 years; $p < 0.001$), with a lower proportion of female patients in the COVID-19 group (41.1% vs. 80.5%; $p < 0.001$). Functional status prior to stroke onset was significantly different, with a lower proportion of functional independence in the COVID-19 group (mRS score 0–2: 65.6% vs. 96.2%; $p < 0.001$ [Table 1]).

Comorbidities

Chronic heart disease (18.9% vs. 34.4%; $p < 0.001$) and atrial fibrillation (21.2% vs. 38.2%; $p < 0.001$) were less common in patients with COVID-19, while chronic liver disease (6.0% vs. 2.5%; $p = 0.022$) and type 2 diabetes mellitus (29.5% vs. 22.3%; $p = 0.014$) were more common. Hypertension, chronic lung disease and chronic kidney disease frequency did not differ between the groups (Table 1).

COVID-19 characteristics

The severity of COVID-19 at stroke onset was moderate in 73.3% of cases, severe in 14.8% and critical in 11.9%. Cough was the most frequent presenting symptom (48.7%), followed by fever (45.9%), pneumonia (14.4%), and acute respiratory distress syndrome (20.0%). COVID-19 diagnosis was established in 66.1% of the patients prior to stroke onset. The mean duration between COVID-19 symptoms and stroke onset was 8.8 ± 11.4 days, and in 33.9% of the COVID-19 group, stroke was the initial manifestation of the COVID-19 disease.

Stroke characteristics

Cardioembolic etiology represented a lower proportion in the COVID-19 group (12.9% vs. 49.6%), while large vessel atherosclerosis (37.6% vs. 16.5%) and cryptogenic stroke (16.8% vs. 0.0%) were observed at a higher proportion in the COVID-19 group ($p < 0.001$). The mean Albert Stroke Program Early Computed Tomography Score (ASPECTS) at admission was lower in the COVID-19 group (7.8 ± 2.4 vs. 8.9 ± 1.5; $p < 0.001$). The mean number of involved vessels was comparable between the COVID-19 and non-COVID-19 groups (1.4 ± 0.9 vs. 1.3 ± 0.5; $p = 0.236$). The detailed distribution of affected vessels is shown in Table 2.

Stroke treatment

The mean duration of time from last known normal to access was shorter in the COVID-19 group (357.4 ± 513.3 min vs. 474.4 ± 365.1 min; $p = 0.009$), while the mean door-to-arterial access duration

TABLE 1 Baseline characteristics of the patients with large vessel occlusion with and without COVID-19

Variables	Non-COVID-19 (*N* = 395)	COVID-19 (*N* = 302)	Total (*N* = 697)	*p*
Mean (SD) age, years	71.0 (15.8)	61.1 (15.7)	67.1 (16.5)	<0.001*
Gender: female, *n* (%)	318 (80.5)	124 (41.1)	442 (63.4)	<0.001*
Pre-admission mRS score 0–2, *n* (%)	380 (96.2)	198 (65.6)	578 (82.9)	<0.001*
Mean (SD) NIHSS score at admission	14.3 (7.5)	17.2 (8.5)	15.4 (8.0)	<0.001*
Hypertension, *n* (%)	271 (68.8)	174 (57.6)	445 (63.8)	0.104
Chronic heart disease, *n* (%)	136 (34.4)	57 (18.9)	193 (27.7)	<0.001*
Chronic lung disease, *n* (%)	76 (19.2)	60 (19.9)	136 (19.5)	0.575
Chronic kidney disease, *n* (%)	43 (10.9)	28 (9.3)	71 (10.2)	0.791
Chronic liver disease, *n* (%)	10 (2.5)	18 (6.0)	28 (4.0)	0.022*
Diabetes mellitus (type 2), *n* (%)	88 (22.3)	89 (29.5)	177 (25.4)	0.014*
Atrial fibrillation, *n* (%)	151 (38.2)	64 (21.2)	215 (30.8)	<0.001*
New onset atrial fibrillation, *n* (%)	0 (0.0)	21 (7.0)	21 (3.0)	0.238

Note: Missing data count per variable: age, *n* = 53; gender *n* = 17; pre-admission mRS score, *n* = 70; NIHSS at admission, *n* = 72; hypertension, *n* = 40; chronic heart disease, *n* = 24; chronic lung disease, *n* = 22; chronic kidney disease, *n* = 24; chronic liver disease, *n* = 22; diabetes mellitus (type 2), *n* = 31; atrial fibrillation, *n* = 31; new onset atrial fibrillation, *n* = 417.

Abbreviations: mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation.

*Statistically significant.

was longer in the COVID-19 group (87.5 ± 63.5 min vs. 71.6 ± 80.0 min; $p = 0.043$). Intravenous tissue plasminogen activator (tPA) administration was less common in the COVID-19 group (23.5% vs. 33.4%; $p < 0.001$). A higher proportion of mechanical thrombectomy procedures was performed under general anesthesia in the COVID-19 group (31.5% vs. 19.1%; $p < 0.001$), while mean thrombectomy pass number (1.8 ± 1.5 vs. 1.9 ± 1.2; $p = 0.520$), first pass effect (53.3% vs. 49.1%; $p = 0.395$), and stenting rates (7.3% vs. 8.6%; $p = 0.584$) were comparable among the two groups (Table 3). The mean duration of the procedure to achieve revascularization was prolonged in the COVID-19 group (62.2 ± 47.3 vs. 51.9 ± 31.9; $p = 0.002$). Moreover, there was a higher proportion of mTICI grade 3 outcomes in the control group (66.6% vs. 25.5%; $p < 0.001$ [Table 3]).

Complications, functional outcomes, and mortality

The procedure-related complication rate was higher among COVID-19 patients (26.6% vs. 10.0%; $p < 0.001$), with 19.7% of the complications in the COVID-19 group being symptomatic. There was no significant difference in sICH (6.6% vs. 5.6%; $p = 0.683$) nor in NIHSS score at 24 h after thrombectomy (11.9 ± 10.8 vs. 12.2 ± 8.2; $p = 0.807$) between the COVID-19 and non-COVID-19 groups.

The length of hospital stay was longer in the COVID-19 group (15.5 ± 17.6 days vs. 8.4 ± 8.5 days; $p < 0.001$). Poor functional outcome (mRS score 3–6) at discharge was observed in a significantly higher proportion of patients in the COVID-19 group (37.1% vs. 9.6%; $p < 0.001$), and favorable functional outcome (mRS 0–2) at 90-day follow-up was observed in a lower proportion of COVID-19 patients versus non-COVID-19 patients (10.6% vs 59.0%; $p < 0.001$). Similarly, the mortality rate was more than twofold higher in the COVID-19 group (42.0% vs. 19.1; $p \leq 0.001$ [Table 3]).

Predictors of revascularization mTICI grade 3

In the univariable model, absence of COVID-19 infection (OR 0.33, 95% CI 0.23–0.48; $p < 0.001$), female gender (OR 2.56, 95% CI 1.78–3.69; $p < 0.001$), and higher ASPECTS (OR 1.15, 95% CI 1.04–1.27; $p = 0.007$) were predictors of better revascularization (mTICI grade 3). Accounting for other possible cofounders, only COVID-19 status (OR 0.30, 95% CI 0.12–0.77; $p = 0.012$) and female sex (OR 2.83, 95% CI 1.31–6.15; $p = 0.008$) were independent predictors (Table 4).

Predictors of unfavorable outcomes (mRS score 3–6)

Unfavorable outcomes were higher with increasing age (OR 1.04, 95% CI 1.02–1.06; $p < 0.001$) and NIHSS score at admission (OR 1.10, 95% CI 1.06–1.15; $p < 0.001$). Accounting for possible confounders (including pre-admission mRS score), age (OR 1.04, 95% CI 1.02–1.06; $p < 0.001$) and NIHSS score (OR 1.10, 95% CI 1.06–1.15; $p < 0.001$) persisted as independent risk factors for unfavorable outcomes (Table 5). A sensitivity analysis including only patients with a pre-admission mRS score of 0–2, found higher rates of unfavorable outcome among COVID-19 patients at 3 months (OR 2.10, 95% CI 1.08–3.99; $p = 0.025$); however, this association was not significant after controlling for other variables (OR 0.81, 95% CI 0.22–2.59; $p = 0.731$ [Table S1]). A summary of predictors of mTICI grade 3 and mRS score 3–6 is presented in Figure S1.

TABLE 2 Summary of the included large vessel occlusions

Variables	Non-COVID-19 (*N* = 395)	COVID-19 (*N* = 302)	Total (*N* = 697)	*p*
Stroke classification, *n* (%)				
Large vessel atherosclerosis (50% or more narrowing in an artery)	64 (16.5)	76 (37.6)	140 (23.8)	<0.001*
Cardioembolic	192 (49.6)	26 (12.9)	218 (37.0)	
Other (dissection, hypercoagulable)	131 (33.8)	66 (32.7)	197 (33.5)	
Cryptogenic	0 (0.0)	34 (16.8)	34 (5.8)	
Mean (SD) number of vessels involved	1.3 (0.5)	1.4 (0.9)	1.4 (0.8)	0.236
Vessel involved, *n* (%)				
ICA	35 (9.0)	9 (25.7)	44 (10.4)	<0.001*
MCA (M1 segment)	156 (40.2)	3 (8.6)	159 (37.6)	
MCA (M2 segment)	89 (22.9)	3 (8.6)	92 (21.7)	
ACA (A1 segment)	4 (1.0)	3 (8.6)	7 (1.7)	
ACA (A2 segment)	4 (1.0)	15 (42.9)	19 (4.5)	
Extracranial carotid	62 (16.0)	0 (0.0)	62 (14.7)	
Basilar	24 (6.2)	2 (5.7)	26 (6.1)	
MCA (M3/4 segments)	10 (2.6)	0 (0.0)	10 (2.4)	
Vertebral	4 (1.0)	0 (0.0)	4 (0.9)	
Second vessel involved (if more than one), *n* (%)				
ICA	7 (8.5)	4 (7.4)	11 (8.1)	0.002*
MCA (M1 segment)	39 (47.6)	10 (18.5)	49 (36.0)	
MCA (M2 segment)	18 (22.0)	8 (14.8)	26 (19.1)	
ACA (A1 segment)	5 (6.1)	13 (24.1)	18 (13.2)	
ACA (A2 segment)	3 (3.7)	4 (7.4)	7 (5.1)	
Extracranial carotid	0 (0.0)	3 (5.6)	3 (2.2)	
Basilar	1 (1.2)	1 (1.9)	2 (1.5)	
PCA	2 (2.4)	6 (11.1)	8 (5.9)	
MCA (M3/4 segments)	6 (7.3)	4 (7.4)	10 (7.4)	
Vertebral	1 (1.2)	1 (1.9)	2 (1.4)	
Third vessel involved (if more than two), *n* (%)				
MCA (M1 segment)	6 (31.6)	2 (50.0)	8 (34.8)	0.149
MCA (M2 segment)	5 (26.3)	1 (25.0)	6 (26.1)	
ACA (A1 segment)	7 (36.8)	0 (0.0)	7 (30.4)	
ACA (A2 segment)	1 (5.3)	0 (0.0)	1 (4.3)	
PCA	0 (0.0)	1 (25.0)	1 (4.3)	
Fourth vessel involved (if more than three), *n* (%)				
MCA (M1 segment)	0 (0.0)	8 (42.1)	8 (36.4)	0.244
MCA (M2 segment)	3 (100.0)	7 (36.8)	10 (45.5)	
ACA (A1 segment)	0 (0.0)	3 (15.8)	3 (13.6)	
PCA	0 (0.0)	1 (5.3)	1 (4.5)	

Note: Missing data count per variable: stroke classification, *n* = 108; ASPECTS, *n* = 152; vessel involved, *n* = 273.

Abbreviations: ACA, anterior cerebral artery; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; COVID-19, coronavirus disease 2019; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; SD, standard deviation.

*Statistically significant.

DISCUSSION

Our global collaborative effort to pool data on patients with LVO during the COVID-19 pandemic provided us with the opportunity to explore the impact of COVID-19 on interventional outcomes in this population. From analyses of compiled cases from 50 institutions worldwide, our data suggest that COVID-19 patients with concomitant LVO have poorer functional outcome and rates of

TABLE 3 Summary of the procedures performed and outcomes

Variables	Non-COVID-19 (*N* = 395)	COVID-19 (*N* = 302)	Total (*N* = 697)	*p*
Mean (SD) door to groin time, min	71.6 (80.0)	87.5 (63.5)	76.7 (75.4)	0.043*
Mean (SD) LKN to groin time, min	474.4 (365.1)	357.4 (513.3)	442.8 (413.1)	0.009*
tPA given, *n* (%)	132 (33.4)	71 (23.5)	203 (29.1)	<0.001*
Mean (SD) number of passes during thrombectomy	1.9 (1.2)	1.8 (1.5)	1.8 (1.3)	0.520
First pass effect, *n* (%)	194 (49.1)	161 (53.3)	279 (40.0)	0.395
Stenting, *n* (%)	34 (8.6)	22 (7.3)	56 (8.0)	0.584
Mean (SD) procedure duration, min	51.9 (31.9)	62.2 (47.3)	56.4 (39.6)	0.002*
Favorable revascularization (mTICI 2b-3)	337 (85.3)	154 (50.9)	491 (86.3)	<0.001*
Favorable revascularization (mTICI 3)	263 (66.6)	77 (25.5)	340 (48.8)	<0.001*
Complications during or after the procedure, *n* (%)				
None	352 (90.0)	168 (73.4)	521 (83.9)	<0.001*
Asymptomatic	39 (10.0)	16 (6.9)	55 (8.9)	
Symptomatic	0 (0.0)	45 (19.7)	45 (7.2)	
sICH, *n* (%)	22 (5.6)	20 (6.6)	42 (6.0)	0.683
Mean (SD) NIHSS score 24 h post thrombectomy	12.2 (8.2)	11.9 (10.8)	12.1 (9.1)	0.807
mRS score at discharge, *n* (%)				
0–2	131 (33.2)	149 (49.3)	280 (40.2)	<0.001*
3–6	38 (9.6)	112 (37.1)	150 (21.5)	
NA	226 (57.2)	41 (13.6)	267 (38.3)	
mRS score at 3 months follow-up, *n* (%)				
0–2	233 (59.0)	32 (10.6)	265 (38.0)	<0.001*
3–6	73 (18.5)	18 (6.0)	91 (13.1)	
NA	89 (22.5)	252 (83.4)	341 (48.9)	
Mean (SD) length of hospital stay, days	8.4 (8.5)	15.5 (17.6)	15.5 (17.5)	<0.001*
Discharge, *n* (%)				
Home	81 (20.5)	41 (13.6)	122 (17.5)	<0.001*
Rehabilitation	173 (43.8)	56 (18.5)	229 (32.9)	
Hospice	23 (5.8)	5 (1.7)	28 (4.0)	
Nursing facility	57 (14.4)	17 (5.6)	74 (10.6)	
Not reported/deceased	61 (15.4)	183 (60.6)	244 (35.0)	
In-hospital mortality	74 (19.1)	111 (42.0)	185 (28.4)	<0.001*

Note: Missing data count per variable: door to groin, $n = 271$; LKN to groin, $n = 264$; tPA given, $n = 80$; number of passes, $n = 112$; first pass effect, $n = 144$; stenting, $n = 65$; procedure duration, $n = 102$; favorable revascularization, $n = 127$; complications, $n = 75$, sICH, $n = 373$; 24 h NIHSS, $n = 161$; mRS at discharge, $n = 267$; mRS at 3 months; $n = 341$; length of hospital stay, $n = 92$; discharge, $n = 191$.

Abbreviations: LKN, last known normal; mRS, modified Rankin Scale; mTICI, modified Treatment in Cerebral Infarction; NA, not available; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; sICH, symptomatic intracerebral hemorrhage; tPA, tissue plasminogen activator.

*Statistically significant.

revascularization compared to non-COVID-19 patients, with a mortality rate reaching up to 42%. The likelihood of achieving complete revascularization was reduced by 70%, compared to patients without COVID-19, in our collaboration. Our data are supported by contemporary reports of poorer outcomes in patients with AIS in the setting of COVID-19, albeit without controls, which is a key advantage of our current report [24-30]. Similarly to the present study, other analyses also suggest that COVID-19 is an independent predictor of LVO, less favorable functional outcome at follow-up, and increased mortality [19,30,31,32,33].

The underlying pathophysiology that drives poorer outcomes for AIS in COVID-19 patients is subject to ongoing investigation. However, it is likely that COVID-19 influences patient conditioning for post-stroke recovery. Factors known to impede recovery after stroke include patient demographic factors, baseline functional status, and comorbidities [34]. In addition, stroke characteristics including severity

TABLE 4 Logistic regression for possible predictors of complete revascularization in patients with large vessel occlusion during the COVID-19 pandemic (mTICI grade 3)

Predictors	Univariable	Multivariable
	OR (95% CI)	OR (95% CI)
COVID status		
Non-COVID-19	Reference	
COVID-19	0.33 (0.23–0.48, $p < 0.001$*)	0.30 (0.12–0.77; $p = 0.012$*)
Mean (SD) age	1.01 (0.99–1.02; $p = 0.306$)	0.99 (0.97–1.01; $p = 0.223$)
Gender		
Male	Reference	
Female	2.56 (1.78–3.69, $p < 0.001$*)	2.83 (1.31–6.15; $p = 0.008$*)
Pre-admission mRS score		
0–2	Reference	
3–6	1.48 (0.71–3.32; $p = 0.313$)	1.69 (0.35–12.64; $p = 0.547$)
NIHSS score at admission		
Mean (SD)	0.98 (0.96–1.00; $p = 0.064$)	1.00 (0.96–1.05; $p = 0.836$)
Chronic liver disease		
No	Reference	
Yes	1.06 (0.41–2.93; $p = 0.900$)	1.39 (0.30–10.09; $p = 0.701$)
Diabetes		
No	Reference	
Yes	1.19 (0.81–1.77; $p = 0.370$)	2.78 (1.33–6.31; $p = 0.010$*)
ASPECTS on admission		
Mean (SD)	1.15 (1.04–1.27; $p = 0.007$*)	1.14 (0.95–1.38; $p = 0.153$)
Door to groin time (min)		
Mean (SD)	1.00 (0.99–1.00; $p = 0.065$)	1.00 (0.99–1.00; $p = 0.249$)
LKN to groin time (min)		
Mean (SD)	1.00 (1.00–1.00; $p = 0.053$)	1.00 (1.00–1.00; $p = 0.906$)
tPA given		
No	Reference	
Yes	0.92 (0.64–1.31; $p = 0.634$)	0.77 (0.38–1.56; $p = 0.472$)

Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; CI, confidence interval; LKN, last known normal; mRS, modified rankin scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; tPA, tissue plasminogen activator; SD, standard deviation.

*Statistically significant.

and extent of stroke, location of ischemic tissue, time lag to treatment, concomitant pathologies, and other complications all affect post-stroke recovery [34]. The physiological state secondary to COVID-19 appears to further exacerbate damage caused by ischemia [35]. In particular, the heightened prothrombotic and proinflammatory state of COVID-19 may manifest in several ways, including AIS, vasculopathy, myocarditis, arrhythmias, thrombotic microangiopathy, coagulopathy and thrombocytopenia, tropism to endothelial cells via angiotensin-converting enzyme (ACE)-2 receptor, and inhibition of angiotensin (1–7) production [36-61]. It has been proposed that downregulation of ACE-2, leading to both arteriopathy and thrombosis, may play a central role in the development of stroke during COVID-19 [62-64].

Understanding the characteristics of patients who develop LVO in the setting of COVID-19 is important for prognosis and immediate care. To achieve this, we performed one of the first comparative studies of COVID-19 and control patients with LVO. We found that the mean age of the COVID-19 cohort was younger than that of controls by approximately 10 years, which corroborates prior reported findings from other non-controlled studies [8,27,28,30,31,65,66,67,68]. This apparent incidence is almost fourfold higher than those in the general population. We also found a significantly higher representation of males in the COVID-19 group, which is consistent with previously reported non-controlled studies [28,30].

Elucidating the impact of COVID-19 on the onset and severity of AIS is also an important consideration in the clinical care of this population. This is pertinent, given that 73.3% of the patients who developed LVO with COVID-19 had moderate disease severity according to the WHO classification [21]. Their immune dysregulation may result in a cytokine storm, which is of pathophysiological significance in the development of stroke in COVID-19 disease [69-71]. The time from initial COVID symptomatology to stroke onset was, on average, 9 days in our study [72]. The Global COVID-19 Stroke

TABLE 5 Logistic regression for possible predictors of unfavorable outcomes (modified Rankin Scale score 3–6)

Predictors	Univariable	Multivariable
	OR (95% CI; *p* value)	OR (95% CI; *p* value)
COVID status		
Non-COVID	Reference	
COVID	1.80 (0.94–3.36; $p = 0.071$)	0.82 (0.23–2.59; $p = 0.743$)
Age (years)		
Mean (SD)	1.04 (1.02–1.06; $p < 0.001$*)	1.04 (1.02–1.06; $p < 0.001$*)
Gender		
Male	Reference	
Female	0.96 (0.56–1.69; $p = 0.887$)	1.04 (0.50–2.23; $p = 0.923$)
Pre-admission mRS score		
0–2	Reference	
3–6	2.58 (0.81–7.98; $p = 0.096$)	3.28 (0.93–11.72; $p = 0.061$)
NIHSS score at admission		
Mean (SD)	1.10 (1.06–1.13; $p < 0.001$*)	1.10 (1.06–1.15; $p < 0.001$*)
Chronic liver disease		
No	Reference	
Yes	1.69 (0.43–5.73; $p = 0.413$)	1.80 (0.35–7.84; $p = 0.443$)
Diabetes		
No	Reference	
Yes	1.14 (0.64–1.98; $p = 0.653$)	0.95 (0.48–1.85; $p = 0.894$)
ASPECTS on admission		
Mean (SD)	0.92 (0.81–1.05; $p = 0.206$)	0.96 (0.82–1.14; $p = 0.640$)
tPA given		
No	Reference	
Yes	0.87 (0.51–1.45; $p = 0.588$)	0.82 (0.44–1.49; $p = 0.515$)

Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; COVID-19, coronavirus disease 2019; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator; SD, standard deviation.

*Statistically significant.

Registry reported a similar latency of approximately 7 days between symptom onset and stroke [30]. The interval from symptom onset to hospital presentation was lower in the COVID-19 group, which may be consistent with previous studies that did not show a delay in endovascular thrombectomy time metrics during the COVID-19 era [73,74]. Factors that can increase the risk of stroke include infection, which can also concurrently worsen the severity of the stroke [75].

There was a significant difference between stroke classification according to TOAST criteria, with a higher proportion of patients with cryptogenic stroke in the COVID-19 group [22]. In our international experience, we found that stroke severity was generally worse in the COVID-19 cohort compared to controls, based on ASPECTS, NIHSS score at presentation, and the number of involved vessels. The etiology of strokes for patients with and without COVID-19 was also significantly different. Confirming the preliminary conclusions of smaller non-controlled studies, we found that COVID-19 LVO was associated with higher rates of strokes due to large vessel atherosclerosis or cryptogenic etiology, whereas non-COVID-19 LVO was more likely to be cardioembolic in etiology [18,76,77]. This further supports the suggestion that COVID-19 is a prothrombotic and proinflammatory systemic state which may induce LVO. Additionally, the cerebral distribution of strokes was also considerably different. Non-COVID-19 strokes were most frequently observed in the MCA-M1 distribution. However, COVID-19 LVO appeared more likely to occur in the anterior cerebral artery, for reasons that are yet to be elucidated. It should be noted that a non-negligible portion of the occlusion location data was not available in the current study.

When comparing our experience with those of other large analyses, we found that the Get With The Guidelines-Stroke (GWTG-Stroke) registry analysis reported comparable results in patients diagnosed with COVID-19. The authors reported a worse NIHSS score at presentation, and considerably greater proportions of patients with LVO stroke [31]. In our study, the rate of tPA administration was higher amongst non-COVID-19 patients. This may be related to several factors, but one contributor could have been barriers to stroke care for COVID-19 patients. Consistent with other clinical cerebrovascular studies, there was a relative global decline in intravenous thrombolysis, mechanical thrombectomy, ruptured aneurysm treatment, and aneurysmal subarachnoid hemorrhage admissions during the initial wave of the COVID-19 pandemic [15,78].

The complexity of intervention and technical approach are other factors to be considered for mechanical thrombectomy for LVO. We assessed relative complexity between COVID-19 and non-COVID-19 groups by comparing indirect measures based on the duration of the procedure, number of vessels involved, number of passes, rate of complete and favorable revascularization, and technical complications. Our analysis suggests that having LVO with COVID-19 was associated with more involved vessels, longer procedure duration, and a lower rate of complete revascularization at the end of the procedure, albeit with a similar number of passes per occlusion. Furthermore, COVID-19 patients had a 70% lower likelihood of achieving mTICI grade 3. Our results are in line with those reported in prior non-controlled COVID-19 series and are consistent with historic mechanical thrombectomy data [8,67,68]. A possible explanation is the hypercoagulable state in COVID-19 patients, which may cause re-occlusion. In addition, among the COVID-19 patients undergoing thrombectomy, the intravascular clots were prone to fragment and migrate into both new vascular territories and into distal downstream vasculature, at higher rates than are otherwise typical. However, neither of these possible causes emerged as a pattern or were of a frequency great enough to be generalizable. A prospective, large-scale trial could help to answer such a question. Although we found the initial admission ASPECTS to be highly associated with successful revascularization, the association was not significant in the multivariate model. In the same context, time to groin puncture and whether or not tPA was given were also non-influential factors for revascularization in multivariable analysis. Of note, patients with diabetes had 2.78 higher odds of achieving mTICI grade 3 compared to controls, even after adjustment. The reason for the association with diabetes is unknown but possible hypotheses surround differences in etiology of stroke. Diabetic patients may have received treatment for more strict glycemic control, whereas, paradoxically, non-diabetic patients can encounter iatrogenic hyperglycemia with common COVID treatments such as dexamethasone. As a known inhibitor of fibrinolysis, hyperglycemia on admission was the only independent predictor of failed recanalization after tPA treatment [79,80].

Finally, we compared follow-up functional outcomes after Endovascular therapy (EVT) in patients with COVID-19 versus those without. We found, in our combined cohort, that good functional outcome at discharge and follow-up were significantly lower in the COVID-19 group. The mortality rate, when compared to prior published data, was significantly higher. Similarly, the GWTG-Stroke consortium and the Global COVID-19 Stroke Registry studies demonstrated that COVID-19 was an independent predictor of poor outcome and death [30,31]. Other factors such as diabetes and chronic liver disease history, admission ASPECTS, and tPA use were not associated with poor functional outcome on follow-up. In our cohort, we found that 24-h sICH and NIHSS scores were not significantly different with or without COVID-19. However, patients with COVID-19 had a prolonged hospital stay, which suggests that other factors prolong the perioperative and subsequent recovery process.

Strengths of this study include the fact that it is the first global multicenter controlled study for LVO in COVID-19. It highlights the value of institutional collaboration in addressing clinical questions in a timely and robust manner. The study also has several limitations. Its retrospective design means there is an element of selection bias, particularly when patients are chosen for mechanical thrombectomy. Due to the stress on resources created by the COVID-19 pandemic, some patients may not have received optimal advanced imaging and clinical follow-up, and, as such, there were missing data for several outcomes. Nevertheless, all missing data were within subsidiary variables. Occasionally, control for some cofounders was not possible due to insufficient data in patient records. Future prospective studies are needed to obtain a higher level of evidence.

In conclusion, COVID-19 was an independent predictor of incomplete revascularization in patients with stroke due to LVO in this controlled study. Patients are more often younger, more often male, and have higher morbidity/mortality rates.

AUTHOR CONTRIBUTIONS

Sherief Ghozy: Data curation (lead); formal analysis (lead); project administration (equal); software (equal); validation (equal); visualization (lead); writing – original draft (lead); writing – review and editing (equal). **Ahmad Sweid:** Conceptualization (equal); formal analysis (equal); methodology (equal); resources (equal); validation (equal); writing – review and editing (equal). **Michel Piotin:** Formal analysis (equal); investigation (equal); methodology (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **Kimon Bekelis:** Conceptualization (equal); data curation (equal); formal analysis (equal); validation (equal); visualization (equal); writing – review and editing (equal). **Nader-Antoine Sourour:** Conceptualization (equal); methodology (equal); resources (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **Eytan Raz:** Conceptualization (equal); methodology (equal); resources (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **Daniel Vela-Duarte:** Investigation (equal); methodology (equal); project administration (equal); validation (equal); visualization (equal); writing – review and editing (equal). **Italo Linfante:** Conceptualization (equal); data curation (equal); resources (equal); validation (equal); writing – review and editing (equal). **Guilherme Dabus:** Methodology (equal); resources (equal); software (equal); validation (equal); writing – review and editing (equal). **Max Kole:** Conceptualization (equal); methodology (equal); validation (equal); visualization (equal); writing – review and editing (equal). **Mario Martnez-Galdmez:** Investigation (equal); methodology (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **Shahid M. Nimjee:** Investigation (equal); methodology (equal); project administration (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal). **Demetrius K. Lopes:** Data curation (equal); formal analysis (equal); methodology (equal); validation (equal); writing – review and editing (equal). **Ameer E. Hassan:** Conceptualization (equal); investigation (equal); methodology (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal). **Peter Kan:** Formal analysis (equal); investigation (equal); methodology (equal);

resources (equal); validation (equal); visualization (equal); writing – review and editing (equal). **Mohammad Ghorbani:** Conceptualization (equal); data curation (equal); software (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **Michael R. Levitt:** Conceptualization (equal); methodology (equal); resources (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal). **Simon Escalard:** Conceptualization (equal); methodology (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **Symeon Missios:** Conceptualization (equal); formal analysis (equal); validation (equal); writing – review and editing (equal). **Maksim Shapiro:** Conceptualization (equal); methodology (equal); validation (equal); visualization (equal); writing – review and editing (equal). **Frederic Clarenion:** Formal analysis (equal); investigation (equal); methodology (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal). **Mahmoud Elhorany:** Data curation (equal); methodology (equal); project administration (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **Rizwan A. Tahir:** Conceptualization (equal); data curation (equal); formal analysis (equal); resources (equal); validation (equal); writing – review and editing (equal). **Patrick P. Youssef:** Data curation (equal); investigation (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal). **Aditya S. Pandey:** Conceptualization (equal); data curation (equal); methodology (equal); resources (equal); validation (equal); writing – review and editing (equal). **Robert M. Starke:** Conceptualization (equal); methodology (equal); project administration (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal). **Kareem El Naamani:** Formal analysis (equal); investigation (equal); methodology (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **Rawad Abbas:** Conceptualization (equal); methodology (equal); project administration (equal); resources (equal); validation (equal); writing – review and editing (equal). **Ossama Yassin:** Conceptualization (equal); data curation (equal); formal analysis (equal); validation (equal); visualization (equal); writing – review and editing (equal). **Jorge Galvan:** Conceptualization (equal); data curation (equal); project administration (equal); resources (equal); software (equal); writing – review and editing (equal). **Joshua T. Billingsley:** Conceptualization (equal); data curation (equal); formal analysis (equal); validation (equal); visualization (equal); writing – review and editing (equal). **Abolghasem Mortazavi:** Data curation (equal); formal analysis (equal); methodology (equal); validation (equal); visualization (equal); writing – review and editing (equal). **Melanie Walker:** Formal analysis (equal); methodology (equal); resources (equal); supervision (equal); validation (equal); writing – review and editing (equal). **Mahmoud Dibas:** Data curation (equal); methodology (equal); project administration (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **Fabio Settecase:** Data curation (equal); investigation (equal); methodology (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **Manraj K.S. Heran:** Conceptualization (equal); data curation (equal); resources (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **Anna L. Kuhn:** Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); validation (equal); writing – review and editing (equal). **Ajit S. Puri:** Formal analysis (equal); methodology (equal); resources (equal); software (equal); validation (equal); writing – review and editing (equal). **B. K. Menon:** Conceptualization (equal); data curation (equal); formal analysis (equal); methodology (equal); validation (equal); writing – review and editing (equal). **Sanjeev Sivakumar:** Conceptualization (equal); formal analysis (equal); methodology (equal); resources (equal); validation (equal); writing – review and editing (equal). **Ashkan Mowla:** Data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); validation (equal); writing – review and editing (equal). **Salvatore DAmato:** Conceptualization (equal); data curation (equal); formal analysis (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **Alicia M. Zha:** Investigation (equal); methodology (equal); project administration (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **Daniel Cooke:** Data curation (equal); methodology (equal); project administration (equal); resources (equal); validation (equal); writing – review and editing (equal). **Justin E. Vranic:** Conceptualization (equal); methodology (equal); resources (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **Robert W. Regenhardt:** Investigation (equal); methodology (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal). **James D. Rabinov:** Conceptualization (equal); data curation (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **Christopher J. Stapleton:** Formal analysis (equal); methodology (equal); resources (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **Mayank Goyal:** Data curation (equal); investigation (equal); methodology (equal); validation (equal); visualization (equal); writing – review and editing (equal). **Hannah Wu:** Investigation (equal); methodology (equal); project administration (equal); resources (equal); validation (equal); writing – review and editing (equal). **Jake Cohen:** Methodology (equal); project administration (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal). **David Turkel-Parella:** Investigation (equal); methodology (equal); project administration (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **Andrew Xavier:** Data curation (equal); formal analysis (equal); methodology (equal); resources (equal); validation (equal); writing – review and editing (equal). **Muhammad Wagas:** Data curation (equal); methodology (equal); resources (equal); software (equal); validation (equal); writing – review and editing (equal). **Vincent Tutino:** Conceptualization (equal); methodology (equal); software (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **Adnan H Siddiqui:** Conceptualization (equal); methodology (equal); software (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **Gaurav Gupta:** Conceptualization (equal); data curation (equal); formal analysis (equal); project

administration (equal); validation (equal); writing – review and editing (equal). **Anil Nanda:** Conceptualization (equal); investigation (equal); methodology (equal); project administration (equal); validation (equal); writing – review and editing (equal). **Priyank Khandelwal:** Investigation (equal); methodology (equal); project administration (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **Cristina Tiu:** Conceptualization (equal); data curation (equal); formal analysis (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **Pere Cardona:** Conceptualization (equal); methodology (equal); software (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **Natilia Perez de la Ossa:** Investigation (equal); methodology (equal); resources (equal); software (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **Xabier Urra:** Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); validation (equal); writing – review and editing (equal). **Mercedes De Lera Alfonso:** Conceptualization (equal); investigation (equal); methodology (equal); project administration (equal); validation (equal); writing – review and editing (equal). **JF Arenillas:** Data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); validation (equal); writing – review and editing (equal). **Marc Ribo:** Conceptualization (equal); formal analysis (equal); investigation (equal); resources (equal); validation (equal); writing – review and editing (equal). **Manuel Requena:** Data curation (equal); investigation (equal); methodology (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **Mariangela Piano:** Formal analysis (equal); methodology (equal); validation (equal); visualization (equal); writing – review and editing (equal). **Guglielmo Pero:** Conceptualization (equal); data curation (equal); formal analysis (equal); validation (equal); visualization (equal); writing – review and editing (equal). **Keith De Sousa:** Data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); validation (equal); writing – review and editing (equal). **Fawaz Al-Mufti:** Conceptualization (equal); investigation (equal); software (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **Zafar Hashim:** Data curation (equal); investigation (equal); software (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **Sanjeev Nayak:** Conceptualization (equal); data curation (equal); formal analysis (equal); methodology (equal); validation (equal); writing – review and editing (equal). **Leonardo Renieri:** Conceptualization (equal); methodology (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal). **Rose Du:** Conceptualization (equal); formal analysis (equal); methodology (equal); resources (equal); software (equal); validation (equal); writing – review and editing (equal). **Mohamed A. Aziz-Sultan:** Data curation (equal); formal analysis (equal); methodology (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **David Liebeskind:** Conceptualization (equal); data curation (equal); methodology (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **R.G. Nogueira:** Conceptualization (equal); data curation (equal); formal analysis (equal); methodology (equal); validation (equal); writing – review and editing (equal). **Mohamad Abdalkader:** Conceptualization (equal); methodology (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **Thanh N Nguyen:** Conceptualization (equal); formal analysis (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **Nicholas Vigilante:** Conceptualization (equal); data curation (equal); investigation (equal); resources (equal); validation (equal); writing – review and editing (equal). **James E. Siegler:** Formal analysis (equal); methodology (equal); project administration (equal); validation (equal); visualization (equal); writing – review and editing (equal). **Jonathan A Grossberg:** Conceptualization (equal); formal analysis (equal); investigation (equal); validation (equal); visualization (equal); writing – review and editing (equal). **Hassan Saad:** Investigation (equal); methodology (equal); project administration (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **Michael R. Gooch:** Conceptualization (equal); data curation (equal); methodology (equal); resources (equal); validation (equal); writing – review and editing (equal). **Nabeel A. Herial:** Conceptualization (equal); investigation (equal); project administration (equal); resources (equal); validation (equal); writing – review and editing (equal). **Robert H. Rosenwasser:** Conceptualization (equal); formal analysis (equal); methodology (equal); validation (equal); visualization (equal); writing – review and editing (equal). **Stavropoula Tjoumakaris:** Conceptualization (lead); methodology (lead); supervision (lead); validation (lead); writing – review and editing (lead). **Aman B. Patel:** Conceptualization (lead); formal analysis (equal); investigation (lead); methodology (lead); validation (lead); visualization (lead); writing – original draft (lead); writing – review and editing (lead). **Ambooj Tiwari:** Conceptualization (lead); formal analysis (lead); supervision (lead); validation (lead); writing – original draft (lead); writing – review and editing (lead). **Pascal M. Jabbour:** Conceptualization (lead); formal analysis (lead); supervision (lead); validation (lead); writing – original draft (lead); writing – review and editing (lead).

CONFLICT OF INTEREST

There are no relevant conflicts of interest.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

All procedures in the studies involving human participants were performed according to our institutional review board ethical standards and national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol was reviewed and approved by our

University Institutional Review Board. Based on our institutional guidelines, all protected health information was removed, and individual patient consent was not required in the analysis of this case series.

ORCID

Adam A. Dmytriw https://orcid.org/0000-0003-0131-5699
Sherief Ghozy https://orcid.org/0000-0001-5629-3023
Simon Escalard https://orcid.org/0000-0003-1306-1008
Mahmoud Elhorany https://orcid.org/0000-0002-0257-2040
Manuel Requena https://orcid.org/0000-0002-5671-6484

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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